GABA and Dynamic Chloride Regulation in Health and Disease

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## Disclosure

<table>
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<tr>
<th>Name of Commercial Interest</th>
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American Epilepsy Society Annual Meeting
I. Physiological aspects of chloride regulation

GABA excites immature neurons
Developmental reduction of $[\text{Cl}^-]$.


Seizures, insults
Developmenatal reduction of $[\text{Cl}^-]_i$

1. GABA depolarizes and excites immature neurons
2. GABA exerts a trophic role mediated by the large calcium influx produced

A sequential maturation of chloride co-transporters

Abrupt loss of [Cl]$_i$ during delivery: an oxytocine mediated protection of the newborn’s brain

Tyzio et al. Science, 2006
An analgesic action of oxytocine during delivery mediated by \([\text{Cl}]_i\)
An analgesic action of oxytocine during delivery mediated by \([\text{Cl}_i]\).

1. Oxytocine receptors antagonists aggravate pain in pups; this is mediated by alterations of \([\text{Cl}_i]\) in pain pathways.

2. Effects mimicked by a diuretic.

3. Important clinical implications.

GABA orchestrates the generation of early patterns
A developmental sequence of patterns (neocortex, hippocampus, striatum)

Calcium spike (Embryo)
10 mV
5% DF/F
1s

Calcium Plateaux (PN)
20 mV
20% DF/F
5s

GDP: PN later
50 mV
20% DF/F
1s

How to identify the conductor?
The conductors are GABAergic neurons

Bonifazi et al, Science, 2009
1. GABAergic neurons orchestrate the earliest patterns

2. The conductors GABAergic neurons are born earlier than other neurons

3. Drugs that alter them will have deleterious actions

Bonifazi et al, Science, 2009
II. Pathological aspects of chloride regulation

Seizures beget seizures and exacerbate excitatory GABA
Seizures beget seizures in an in vitro model of chronic seizures

The intact interconnected hippocampi

Khalilov et al., Neuron 1997

Seizures propagate

Field 1 (ipsi-)
ACSF + KA
ACSF
ACSF

Field 2 (contra-)

An epileptic mirror focus is formed

Khalilov et al., Nature Neuroscience, 2003

1. Increase of intracellular chloride in the Mirror Focus

2. GABA generates more spikes in the Mirror focus

Khalilov et al., Neuron 2005
Failure of chloride removal due to an internalisation of KCC2:

Nardou et al submitted
PB blocks early seizures & aggravates late ones

Inaugurating seizures

PB augments excitatory actions of GABA in the Mirror Focus

Nardou et al submitted
Therefore

1. Chloride levels are highly susceptible to recurrent seizures & readily accumulate in epileptic neurons

2. A variety of lesions are also associated with increase CLI

3. The efficacy of GABA acting anti epileptic drugs depend on the history of seizures prior to administration
Autism: treatment with a diuretic?
Starting point

- Autistic children have often paradoxical reactions to valium and GABA acting agents.

- Implications? High chloride?

- 5 (3-11 yrs old) IAS children were treated with Bumetanide, 1mg daily, 3 months.

- 5 tests: *Childhood Autism Rating Scale*, *Aberrant Behaviour Checklist*, *Clinical Global Impressions; Repetitive and Restrictive Behaviour and the Regulation Disorder Evaluation Grid*. 
Significant amelioration with 5 tests

Lemonnier and Ben-Ari; Acta Pediatr Scand. 2010
Significant amelioration with 5 tests

1. No side neurological/ biochemical effects
2. Clinical double blind trial -60 children
3. In general, high chloride may be a signature of many developmental disorders

Lemonnier and Ben-Ari ; Acta Pediatr Scand. 2010
III. 2 unifying concepts of brain maturation & developmental disorders

1. The checkpoint theory of the relation between the genetic program and neuronal activity

2. Neuroarcheology: presymptomatic electrical and architectural signatures of migration disorders
Genes & environnement in brain maturation

Ben-Ari & Spitzer TINS 2010
1. At all developmental steps, a signature of the developmental stage

2. This activity checks and confirms the correct execution of the genetic program
The Neuro-archeology theory: a presymptomatic architectural/electrical signature of brain disorders
Ben-Ari TINS 2008

1. Misplaced /misconnected neurons remain with the signature of the preceding stage
2. This impacts on the formation of functional units
3. These events are manifested later by clinical symptoms
DCX RNAi – a migration disorder

A. Represa

Ackman J Neurosci. 2008
Producing a migration disorder with in utero sRNAi

1. Misplaced neurons are « frozen « in an immature state
2. They have aberrant connections and interfere with the wiring of the overlying normo-cortex
3. Novel therapeutic strategies should be based on blicking the immature currents of these misplaced neurons
Roman Tyzio
Ilgam Khalilov
Summi Yamamoto
Romain Nardou
G Chazal
R Khazipov’s team
R Cossart’s team
• Daniela Prayer
• Vienna